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Preload Dependence of Doppler-Derived Indexes of Left Ventricular Diastolic Function in Humans

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To determine the effect of filling pressure on the pattern of left ventricular filling in humans, the mitral flow velocity profile was measured by pulsed wave Doppler echocardiography during right and left heart catheterization in 11 patients before and during nitroglycerin infusion. Nitroglycerin reduced mean arterial pressure from 90 ± 9 to 80 ± 11 mm Hg ($p < 0.001$) and mean pulmonary capillary wedge pressure from 9 ± 4 to 4 ± 2 mm Hg ($p < 0.001$). Cardiac output fell from 6.6 ± 1.5 to 5.5 ± 1.4 liters/min ($p < 0.001$) and heart rate increased from 60 ± 13 to 65 ± 14 beats/min ($p < 0.002$). The time constant of isovolumic relaxation (T_L) decreased from 51 ± 9 to 46 ± 8 ms ($p < 0.01$), indicating faster left ventricular relaxation.

Nitroglycerin altered the Doppler characteristics of the early filling (E) wave but not those of the atrial contraction (A) wave. Peak velocity of the E wave decreased from 56 ± 14 to 44 ± 9 cm/s ($p < 0.001$), peak velocity of the A wave did not change and the ratio of peak velocities of the E and A waves decreased from 0.97 ± 0.33 to 0.77 ± 0.20 ($p < 0.02$). The deceleration of the E wave decreased from 289 ± 138 to 186 ± 71 cm/s^2 ($p < 0.02$). The ratio of velocity-time integral of the A wave to total velocity-time integral (that is, contribution of atrial contraction to total filling) increased from 0.31 ± 0.09 to 0.36 ± 0.08 ($p < 0.03$). Crossover pressure correlated positively with peak velocity of the E wave ($p < 0.007$, $r = 0.56$).

These results indicate that the pattern of left ventricular filling, measured by the Doppler mitral flow velocity profile, is dependent on left ventricular filling pressure. A reduction in the filling pressure changes the flow velocity profile in a manner that mimics the abnormalities previously reported with impairment of left ventricular diastolic function. Therefore, when interpreting Doppler-derived indexes of left ventricular diastolic function, the influence of preload must be taken into account.

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The pattern of left ventricular filling during diastole is determined in part by the diastolic properties of the ventricle (1–5). Characterization of ventricular filling has been used increasingly in recent studies as a measure of left ventricular diastolic properties in disease states (6–9) and to evaluate the effects of therapeutic interventions on diastolic function (9–11). Hemodynamic factors independent of the diastolic properties of the ventricle, however, may also influence the pattern of left ventricular filling (5,12,13). The actions of these factors are complex, remain poorly defined and are often ignored.

From theoretical considerations, the instantaneous velocity of blood flow across the mitral anulus should be related to the instantaneous pressure gradient between the left atrium and the left ventricle (14,15). Previous observations in canine models (12,16) have suggested that the peak volumetric filling rate is dependent in part on the left atrial pressure. However, few and conflicting data exist regarding the effect of filling pressure on the pattern of left ventricular filling in humans. Using radionuclide ventriculography, Magorien et al. (13) found that intravenous nitroglycerin, which reduced the left ventricular end-diastolic pressure, did not alter the peak filling rate normalized to the left ventricular end-diastolic volume. On the other hand, McKay et al. (17), in a recent preliminary report, indicated that intravenous nitroglycerin reduced the normalized peak filling rate, also measured by radionuclide ventriculography.

Pulsed wave Doppler echocardiography is a relatively new technique that allows noninvasive measurement of the

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instantaneous velocity of blood flow across the mitral anulus, without requiring irradiation or producing hemodynamic effects (18,19). This technique has been used increasingly to characterize abnormal left ventricular filling patterns in a variety of cardiac diseases (20–25). The effects of a reduction in left ventricular filling pressure on the velocity of blood flow across the mitral valve and on the distribution of transmitral flow during diastole have not previously been determined in humans. A clear understanding of these effects is important for the correct interpretation of normal and abnormal left ventricular filling patterns in relation to the intrinsic diastolic properties of the ventricle. The purpose of this study is to examine the effects of a reduction in left ventricular filling pressure by nitroglycerin infusion on the pattern of the Doppler mitral flow velocity profile in humans, and to relate these changes to invasive hemodynamic measurements.

Methods

Study patients (Table 1). Eleven patients (seven male, four female; mean age 57 years, range 43 to 78) undergoing cardiac catheterization for the evaluation of chest pain formed the study group. Nine patients had significant coronary artery disease (≥50% reduction in diameter); six of the nine had had previous myocardial infarction. Two patients had normal coronary arteries and one of these had definite previous infarction documented by typical electrocardiographic and serum enzyme changes and inferior akinesia on the left ventriculogram. No patient had evidence of mitral regurgitation on left ventriculography, or Doppler evidence of aortic regurgitation. The study was approved by the Subcommittee on Human Studies of the Massachusetts General Hospital, and written informed consent was obtained from all patients.

Study protocol. All measurements were made in the cardiac catheterization laboratory. Nitrates were withheld 12 hours before catheterization except in two patients in whom nitrates were continued because of the severity of angina (Patient 7) or insufficient time between hospital admission and catheterization (Patient 8). Other medications, including beta-adrenergic blockers and calcium channel blockers, were continued. On the morning of the study, a preliminary echocardiographic examination was performed to determine whether images of sufficient quality could be obtained, and to familiarize the operator with the technical aspects of the individual study. Standard premedication (diazepam, 5 to 10 mg, and diphenhydramine, 25 to 50 mg orally) for routine catheterization was given. Right heart catheterization was performed with a 7F triple lumen balloon-tipped thermodilution catheter and left heart catheterization with a 7F angiographic micromanometer catheter (Millar Instruments) inserted from the groin by the Seldinger technique.

After baseline hemodynamic and echocardiographic measurements were made, nitroglycerin was infused at an initial rate of 25 μg/min, and the rate was titrated upward to decrease the mean pulmonary capillary wedge pressure by approximately 5 mm Hg, taking care to avoid undue hypotension. When a stable steady state was achieved, hemodynamic and echocardiographic measurements were repeated.

Hemodynamic data. Hemodynamic measurements were made with the patient supine. Pressures were referenced to atmospheric pressure at the level of the midchest. The time derivative of left ventricular pressure (dP/dt) was obtained by electronic differentiation. Systemic arterial pressure was measured through the side arm of a femoral artery introducer. Cardiac output was measured by the thermodilution technique. Stroke volume and systemic vascular resistance were calculated using standard formulas (26). The time con-

Table 1. Clinical Data in 11 Patients

Patient No.	Age (yr) & Sex	Percent Diameter Coronary Artery Stenosis	Contrast Left Ventricular Angiogram
1	78 F	100% LAD, 100% RCA	Anteroapical akinesia/dyskinesia
2	55 M	99% LAD	Anterior hypokinesia
3	63 F	Normal	Inferior akinesia
4	50 F	100% LAD, 50% RCA	Anterior hypokinesia
5	60 M	95% LAD, 100% LCx marginal, 60% RCA	Apical akinesia, anterolateral and inferior hypokinesia
6	49 M	95% LCx marginal, 70% RCA	Inferior akinesia
7	49 M	60% LCx marginal, 50% RCA	Normal
8	51 F	Normal	Normal
9	67 M	70% LCx marginal	Normal
10	60 M	100% LAD	Anterolateral hypokinesia
11	43 M	80% LAD, 70% LCx	Anterior hypokinesia

LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery.

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stants of isovolumic relaxation (T_L and T_D) were obtained by digitizing the left ventricular pressure tracing from the point of peak negative dP/dt to a point 5 mm Hg above the end-diastolic pressure (27,28). T_L was defined as the negative reciprocal of the slope relating the natural logarithm of the isovolumic left ventricular pressure to time (27); this method assumes a zero pressure asymptote. T_D was defined as the negative reciprocal of the slope relating dP/dt to pressure, allowing for a nonzero pressure asymptote (P_B) (28). The values for three consecutive cardiac cycles were averaged.

Echocardiographic data. Echocardiographic data were recorded on an Advanced Technology Laboratories Mark 600 ultrasound imager equipped with a 3 MHz mechanical transducer. The size of the Doppler sample volume was set at an axial length of 3 mm. A "wall filter" setting of 400 Hz was used. Two-dimensional echocardiographic images were recorded on ½ inch (1.27 cm) videotape, and Doppler signals were recorded on ½ inch videotape and simultaneously printed at a paper speed of 100 mm/s.

To obtain optimal echocardiographic images, all patients were rotated to the left by 30°, as measured by the rotary mechanism of the catheterization table. A standard four chamber view of the heart from the apical window was recorded first. Minor adjustments to the transducer position were made to maximize the mediolateral diameter of the mitral anulus. Pulsed wave Doppler measurements were then obtained with the Doppler beam aligned perpendicular or nearly perpendicular to and bisecting the plane of the mitral anulus, and with the Doppler sample volume placed just on the left ventricular side of the plane of the anulus (Fig. 1). Small adjustments were made to the transducer angulation to obtain the highest peak velocity of the early filling (E) wave. Because the Doppler beam was perpendicular or nearly perpendicular to the plane of the mitral anulus, no angle correction of the Doppler signals was made.

Recordings were made during quiet respiration. Great care was taken to ensure that, for the control and nitroglycerin studies, the patient was rotated to the same degree, the transducer was placed at the same location on the chest wall and the relation of the Doppler sample volume to the mitral anulus was constant.

The diameter of the mitral anulus was measured from the video frame containing maximal separation of the mitral leaflets (second or third frame after mitral valve opening) using a commercially available analysis system (Microsonics CAD 886 System, Microsonics Inc.) Mitral anulus area was calculated by assuming a circular orifice (Area = $\pi \times D^2/4$) (29), where D = diameter of the mitral anulus.

Doppler signals were digitized from the paper printouts using the Microsonics analysis system. The ascending limb of the E wave and the descending limb of the atrial contraction (A) wave were linearly extrapolated to the baseline. The velocity signals that occurred during periods of diastasis were also digitized. For each control or nitroglycerin study, the three velocity profiles containing the highest peak E wave velocities were analyzed and averaged. The peak velocities of the E wave and the A wave, the acceleration and deceleration of the E wave (defined as the slope of the ascending and the descending limb of the E wave, respectively), the velocity-time integrals of the E wave and the A wave (obtained by digitizing the modal velocity, that is, the darkest line on the Doppler spectrum), the time from the onset of mitral flow to the peak velocity of the E wave, the duration of the E wave and the total duration of left ventricular filling were measured (Fig. 2). A representative pair of Doppler signals taken from a control study and from the corresponding nitroglycerin study are illustrated in Figure 3.

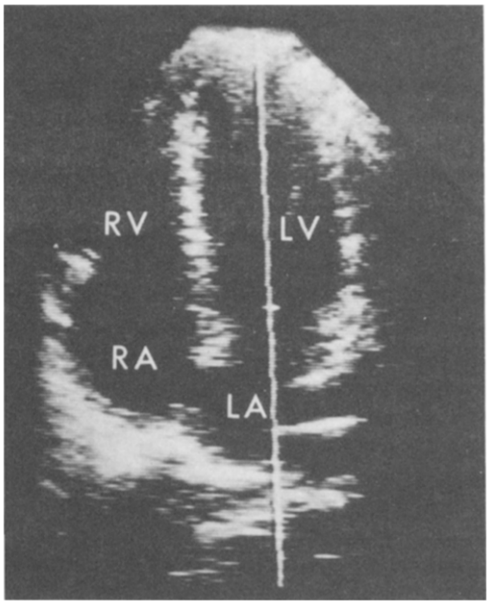


Figure 1. A typical apical four chamber echocardiographic cross-sectional image demonstrating the alignment of the Doppler ultrasound beam (**long vertical line**) and the position of the Doppler sample volume (**short horizontal line**) in this study. The Doppler ultrasound beam is aligned as close to perpendicular as possible to the mitral anulus plane. The sample volume is located just on the left ventricular side of the mitral anulus plane in diastole. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

For each Doppler profile analyzed, the following derived values were obtained: 1) the ratio of the peak velocities of the E and A waves; 2) the total velocity-time integral, obtained by summing the velocity-time integrals of the E wave, diastasis and A wave; 3) the contribution of the E and A waves to total filling, calculated by dividing the component velocity-time integral by the total velocity-time integral; and 4) the peak velocity of the E wave normalized to the total velocity-time integral, to obtain a variable equivalent to the peak volumetric filling rate of the early filling phase normalized to stroke volume.

Filling volume was calculated by multiplying the total velocity-time integral by the mitral anulus area, and was

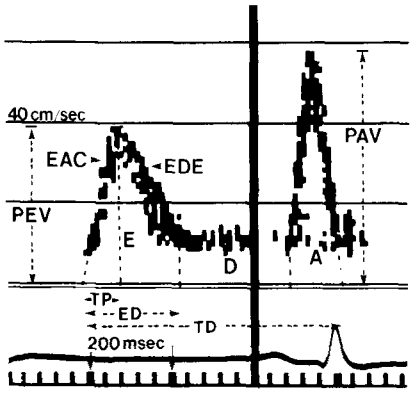


Figure 2. An example of a spectral display of the Doppler mitral flow velocity profile, demonstrating the various characteristics of the profile that were measured. A = A (atrial contraction) wave; D = diastasis; E = E (early filling) wave; EAC = acceleration (upward slope) of the E wave; EDE = deceleration (downward slope) of the E wave; ED = E wave duration; PAV = peak A wave velocity; PEV = peak E wave velocity; TD = total duration of filling; TP = time to peak velocity of the E wave. The velocity-time integrals of the E wave, A wave and diastasis were obtained by digitizing their areas.

compared with the stroke volume measured by thermodilution. Peak volumetric filling rate during the early filling phase was obtained by multiplying the peak velocity of the E wave by the mitral anulus area.

Statistical analysis. Data are expressed as mean ± SD. All measurements in the control and nitroglycerin studies were compared using Student's paired *t* test. Echocardiographic and hemodynamic measurements were related by least squares linear regression analysis. Differences were considered significant if probability (p) for acceptance of the null hypothesis was <0.05.

Results

Hemodynamic data (Table 2). The mean rate of nitroglycerin infusion was 141 μg/min (range 50 to 400). Nitroglycerin reduced left ventricular peak systolic pressure, mean arterial pressure, left ventricular end-diastolic pressure and left ventricular minimal pressure. Mean pulmonary capillary wedge pressure fell from 9 ± 4 to 4 ± 2 mm Hg ($p < 0.001$), and the *V* wave of the wedge pressure (equivalent to the pressure at mitral valve opening or "crossover" pressure) fell from 12 ± 4 to 5 ± 2 mm Hg ($p < 0.001$). Heart rate increased from 60 ± 13 to 65 ± 14 beats/min ($p < 0.002$) and cardiac output and stroke volume decreased.

Nitroglycerin decreased the absolute value of peak negative dP/dt from 1,526 ± 403 to 1,250 ± 305 mm Hg/s ($p < 0.001$). T_L fell by a small but statistically significant amount from 51 ± 9 to 46 ± 8 ms ($p < 0.01$). T_D also fell, but the difference was not statistically significant.

Doppler flow measurements (Table 3). Nitroglycerin decreased the peak velocity of the E wave from 56 ± 14 to 44 ± 9 cm/s ($p < 0.001$), but did not alter the peak velocity of the A wave (61 ± 16 versus 59 ± 13 cm/s) (p = NS). The ratio of the peak velocities of the E and A waves fell from 0.97 ± 0.33 to 0.77 ± 0.20 ($p < 0.02$). Nitroglycerin also reduced the acceleration of the E wave from 789 ± 479 to 548 ± 368 cm/s^2 ($p < 0.004$) and the deceleration of the E wave from 289 ± 138 to 186 ± 71 cm/s^2 ($p < 0.02$).

The velocity-time integral of the E wave decreased from 7.7 ± 1.5 to 6.5 ± 0.9 cm ($p < 0.006$). The velocity-time integral of the A wave did not change. The total velocity-time integral decreased from 14.3 ± 2.7 to 12.3 ± 2.0 cm ($p < 0.002$). As a result, the ratio of the velocity-time integral of the A wave to the total velocity-time integral increased from 0.31 ± 0.10 to 0.36 ± 0.08 ($p < 0.03$).

The time from the onset of transmitral flow to the peak velocity of the E wave and duration of the E wave did not change during nitroglycerin infusion. The total duration of left ventricular filling was shorter in 9 of the 12 patients, but the reduction in the mean values (644 ± 225 ms versus 605 ± 212 ms) was not statistically significant.

Nitroglycerin decreased the mitral anulus area from 7.7 ± 1.8 to 7.1 ± 1.6 cm^2 ($p < 0.001$). The filling volume, obtained from the product of the total velocity time integral and the mitral anulus area, fell from 113 ± 43 ml to 89 ± 32 ml ($p < 0.002$). The filling volumes in the control and nitroglycerin studies correlated well with the stroke volumes measured by thermodilution (Fig. 4). The peak flow rate during the early filling phase, obtained from the product of the peak velocity of the E wave and the mitral anulus area, decreased from 429 ± 134 to 310 ± 102 ml/s ($p < 0.001$).

Correlation of echocardiographic and hemodynamic measurements. For the control and nitroglycerin measurements taken as a group, the crossover pressure correlated

Figure 3. Patient 3. A representative pair of Doppler mitral flow velocity profiles obtained from the control study (**A**) and the corresponding nitroglycerin study (**B**) demonstrating the typical changes in the velocity profile during nitroglycerin infusion.

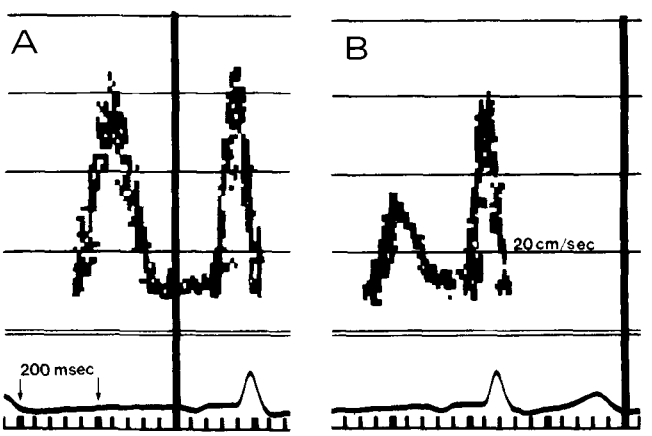


Table 2. Comparison of Hemodynamic Variables in the Control and Nitroglycerin Studies in 11 Patients

	Control	Nitroglycerin	p Value
Heart rate (beats/min)	60 ± 13	65 ± 14	0.002
Pressure (mm Hg)			
Mean arterial	90 ± 9	80 ± 11	0.001
LV peak systolic	129 ± 14	101 ± 13	0.001
LV end-diastolic	15 ± 6	7 ± 3	0.001
LV minimal	5 ± 3	1 ± 3	0.001
Pulmonary wedge *V* wave	12 ± 4	5 ± 2	0.001
Mean pulmonary wedge	9 ± 4	4 ± 2	0.001
Mean right atrial	4 ± 2	2 ± 2	0.005
Cardiac output (liters/min)	6.55 ± 1.49	5.48 ± 1.41	0.001
Stroke volume (ml)	114 ± 33	87 ± 27	0.001
SVR (dynes·s·cm^{-5})	1,108 ± 234	1,182 ± 230	0.03
LV peak +dP/dt (mm Hg/s)	1,359 ± 299	1,392 ± 415	NS
LV Peak −dP/dt (mm Hg/s)	1,526 ± 404	1,251 ± 305	0.001
T_L (ms)	51 ± 9	46 ± 8	0.01
T_D (ms)	72 ± 27	65 ± 17	NS
P_B (mm Hg)	−25 ± 18	−14 ± 11	0.01

dP/dt = first derivative of left ventricular pressure; LV = left ventricular; P_B = nonzero pressure asymptote; SVR = systemic vascular resistance; T_D and T_L = time constants of isovolumic relaxation.

with the peak velocity of the E wave ($p < 0.007$, $r = 0.56$) (Fig. 5). The percent decrease in the peak velocity of the E wave during nitroglycerin infusion tended to correlate with the percent decrease in the mean pulmonary capillary wedge pressure ($p = 0.06$, $r = 0.58$) (Fig. 6), as did the percent decrease in the peak volumetric flow rate of the E wave ($p < 0.05$, $r = 0.62$). These Doppler variables did not, however, correlate with the percent decrease in the crossover pressure.

Discussion

This study demonstrates that a reduction in left ventricular filling pressure by nitroglycerin infusion significantly alters the Doppler mitral flow velocity profile in humans. Although nitroglycerin has, if anything, a favorable effect on early diastolic relaxation (as indicated by the fall in T_L), the changes in the Doppler mitral flow velocity profile mimic those previously reported to be associated with impairment

Table 3. Comparison of Doppler Echocardiographic Variables in the Control and Nitroglycerin Studies

	Control	Nitroglycerin	p Value
Peak E wave velocity (cm/s)	56 ± 14	44 ± 9	0.001
Peak A wave velocity (cm/s)	61 ± 16	59 ± 13	NS
Peak E wave to peak A wave velocity ratio	0.97 ± 0.33	0.77 ± 0.20	0.02
E wave acceleration (cm/s^2)	789 ± 479	548 ± 368	0.004
E wave deceleration (cm/s^2)	289 ± 138	186 ± 71	0.02
E wave velocity-time integral (cm)	7.7 ± 1.5	6.5 ± 0.9	0.006
Diastasis velocity-time integral (cm)	2.2 ± 2.0	1.4 ± 1.4	0.05
A wave velocity-time integral (cm)	4.4 ± 1.2	4.3 ± 0.8	NS
Total velocity-time integral (cm)	14.3 ± 2.7	12.3 ± 2.0	0.002
Percent of E wave to total velocity-time integral (%)	54 ± 8	53 ± 7	NS
Percent of A wave to total velocity-time integral (%)	32 ± 10	36 ± 8	0.03
Peak E wave velocity normalized to total velocity-time integral (s^{-1})	4.02 ± 1.14	3.64 ± 0.90	0.02
Time to peak E wave velocity (ms)	97 ± 31	105 ± 25	NS
E wave duration (ms)	268 ± 72	279 ± 58	NS
Total filling duration (ms)	644 ± 225	605 ± 212	NS

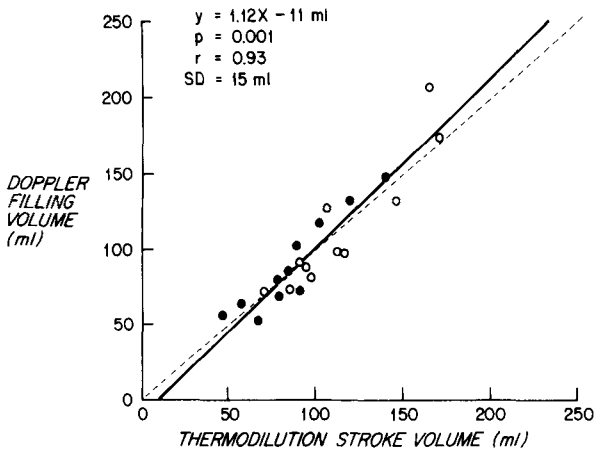


Figure 4. Relation of filling volume measured by combined two-dimensional and Doppler echocardiography to stroke volume measured by thermodilution in the control (**open circles**) and nitroglycerin (**closed circles**) studies. The broken line is the line of identity.

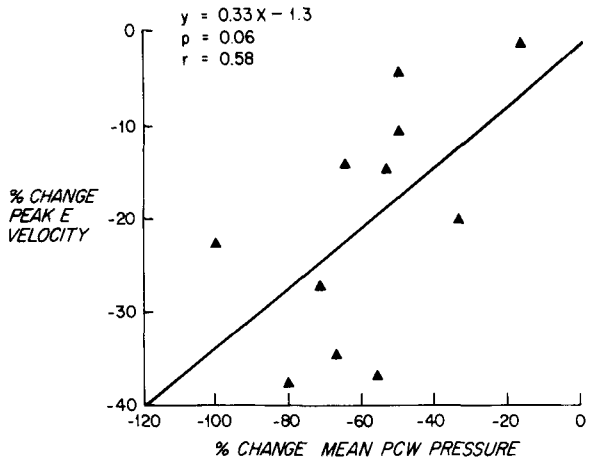
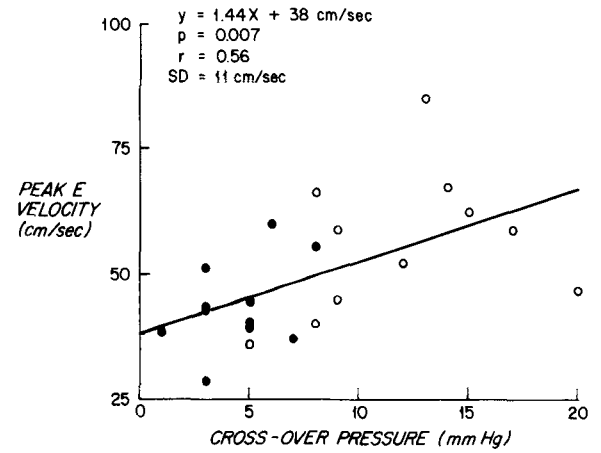


Figure 6. Relation of the percent change in the peak velocity of the E wave during nitroglycerin infusion to the percent change in the mean pulmonary capillary wedge (PCW) pressure.

of diastolic left ventricular function (20–25). These findings underscore the importance of left ventricular filling pressure in determining the pattern of left ventricular diastolic filling, and the need to account for alterations in preload in interpreting changes in Doppler-derived indexes of left ventricular diastolic function.

Despite the widespread use of measurements of filling to describe left ventricular diastolic function, surprisingly little information is available on how filling characteristics relate to the primary diastolic properties of relaxation and passive compliance and how this relation may be modified by hemodynamic factors unrelated to diastolic properties. The early work of Yellin et al. (12) in anesthetized open chest dogs suggested that left ventricular filling rate, measured by an electromagnetic flow probe sewn onto the mitral anulus,

Figure 5. Relation of the crossover pressure (taken from the peak of the V wave of the pulmonary capillary wedge pressure tracing) to the peak velocity of the E wave in the control (**open circles**) and nitroglycerin (**closed circles**) studies.



was dependent on left atrial pressure, which they acutely altered with a surgically constructed shunt between the left ventricle and left atrium. Recently, workers from the same institution (16) reported that volume infusion in conscious dogs increased left atrial pressure and peak transmitral flow rate, which they measured in the same way. Using radionuclide ventriculography in humans, however, Magorien et al. (13) reported that intravenous nitroglycerin did not alter the peak left ventricular filling rate, which was normalized to left ventricular end-diastolic volume. In a more recent preliminary report, McKay et al. (17), also using radionuclide ventriculography, found that intravenous nitroglycerin decreased the peak filling rate normalized to left ventricular end-diastolic volume in humans. The reason for this discrepancy between the studies is unclear. In the study of Magorien et al. the change in the pulmonary capillary wedge pressure during nitroglycerin infusion was not given, so that a comparison of the hemodynamic effects of nitroglycerin in the two studies cannot be made.

Hemodynamic changes during nitroglycerin infusion. In the present study, the hemodynamic changes during nitroglycerin infusion reflected the effects of systemic venodilation and were similar to those previously described by others (30). Right atrial, mean pulmonary capillary wedge, left ventricular minimal, left ventricular end-diastolic and mean aortic pressures decreased. Heart rate increased slightly, presumably as a result of the action of baroreceptor reflexes.

Peak negative dP/dt fell consistently, most likely because of the fall in left ventricular systolic pressure, to which it is highly sensitive (31). The time constant of isovolumic relaxation (T_L) on the other hand, fell significantly, indicating that left ventricular relaxation was faster (27). T_L has been shown to decrease with a reduction in left ventricular end-systolic volume (32), which probably occurred during nitroglycerin infusion (30). Other possible explanations for

the decrease in T_L include faster relaxation due to increased sympathetic stimulation, as suggested by the slightly faster heart rate, or amelioration of ischemia (5).

Changes in Doppler mitral flow velocity profile during nitroglycerin infusion. During nitroglycerin infusion, the peak velocity of the E wave decreased. Because the peak velocity of the A wave did not change significantly, the ratio of the peak velocities of the E and A waves also decreased. Even when the peak velocity of the E wave was normalized to the total velocity-time integral (equivalent to normalizing the peak volumetric filling rate to the filling volume), it remained lower during nitroglycerin infusion. Because nitroglycerin simultaneously reduced the mitral anulus area, probably as a result of the accompanying reduction in left ventricular size (30), the calculated peak volumetric filling rate decreased proportionately more than the peak E velocity alone (-27 versus -20%). This difference highlights the importance of taking into account simultaneous changes in mitral anulus size as well as transmitral flow velocity when assessing the effects of interventions on left ventricular diastolic filling rate. Nitroglycerin also decreased both the acceleration and deceleration of the E wave, but did not significantly alter the time from the onset of transmitral flow to the peak velocity of the E wave or the duration of the E wave.

The Doppler mitral velocity-time integral during diastole reflects the left ventricular filling volume, and cumulative left ventricular filling volume may be calculated by multiplying the instantaneous transmitral flow velocity by the instantaneous mitral anulus area, and integrating the product over time. The mitral anulus diameter was measured at just one point in early diastole, and its value was arbitrarily kept constant throughout diastole to avoid introducing random measurement error into the calculations. Despite the use of this simplified approach, the total filling volumes in both the control and nitroglycerin studies correlated closely with the corresponding stroke volumes measured by thermodilution. Similar correlations using these assumptions have been reported previously from this laboratory and others (29,33). During nitroglycerin infusion, the velocity-time integral of the E wave and the total velocity-time integral decreased, whereas the velocity-time integral of the A wave did not change. As a result, the ratio of the velocity-time integral of the A wave to the total velocity-time integral, and thus the relative contribution of atrial contraction to left ventricular filling, increased significantly.

Pattern of left ventricular filling and abnormal diastolic function. Several characteristics of abnormal left ventricular filling have recently been described by Doppler echocardiography in diseases associated with impaired left ventricular diastolic function. The peak velocity of the E wave and the ratio of the peak velocities of the E and A waves are often decreased in such conditions as hypertrophic cardiomyopathy, dilated cardiomyopathy, secondary hypertrophy, acute left ventricular ischemia and chronic coronary artery disease (20–25). In some of these conditions, there is an accompanying increase in the peak velocity of the A wave (25), reduced deceleration of the E wave (34,35) and an abnormal increase in the contribution of atrial contraction to left ventricular filling (21,22). Thus, many of the changes in the Doppler mitral flow velocity profile during nitroglycerin infusion resemble those that have been associated with impaired left ventricular diastolic function. The peak velocity of the A wave and the time from onset of mitral flow to the peak velocity of the E wave were the only variables previously reported to reflect diastolic function (23,25) that did not change significantly during nitroglycerin infusion. The latter finding agrees with the recent report of Ishida et al. (16), who found that volume infusion in conscious dogs did not alter the time from onset of mitral flow to the peak left ventricular filling rate measured by an electromagnetic flow probe.

Relation of left ventricular filling pressure to the pattern of left ventricular filling. The velocity of transmitral blood flow results directly from the pressure gradient between the left atrium and the left ventricle, and follows a relation described by the Law of Conservation of Energy equation, in which work derived from the pressure gradient is divided into three components, namely, flow acceleration, convective acceleration and viscous losses (14,15). During the passive filling phase, the major determinants of the instantaneous pressure gradient (and hence of blood velocity) between the left atrium and the left ventricle have been postulated to be 1) the crossover pressure, that is, the left atrial and left ventricular pressure at mitral valve opening; 2) the relaxation rate of the left ventricle; 3) the compliance of the left ventricle; 4) the compliance of the left atrium and the pulmonary venous bed; and 5) the size of the mitral anulus (16). A recently developed computer model of left ventricular filling (16) predicted that if all other hemodynamic factors were kept constant, the peak filling rate would increase in a curvilinear relation with the crossover pressure.

The results of this study are consistent with the predictions of this computer model, but the curvilinear relation of crossover pressure to the peak filling rate could not be tested because only two sets of data points were obtained in each patient, and other hemodynamic variables changed simultaneously during nitroglycerin infusion. The crossover pressure correlated modestly with the peak velocity of the E wave, supporting its role as a determinant of the peak velocity, but at the same time suggesting that other factors are also involved. The correlation between the percent decrease in the mean pulmonary wedge pressure during nitroglycerin infusion and the percent decrease in the peak velocity of the E wave was just outside statistical significance, and there was no correlation between the percent decrease in the crossover pressure and the percent decrease in the peak velocity of the E wave. This absence of correlation may be attributed

to simultaneous changes in the other hemodynamic determinants of left ventricular filling, which we were unable to control in this study.

Limitations of the study. Several limitations of this study should be addressed. First, the order of the control and nitroglycerin studies was not randomized. Despite the relatively short half-life of action of intravenous nitroglycerin, the additional time required to perform a control study under stable hemodynamic conditions after the cessation of nitroglycerin infusion was unacceptably long and made a randomized design impractical during left heart catheterization. The hemodynamic changes during nitroglycerin infusion were prominent, and it is unlikely that the changes in echocardiographic measurements that were observed could have resulted from the effect of the passage of time alone.

Second, hemodynamic measurements were made with the patients supine, whereas the corresponding echocardiographic measurements were made immediately afterward with the patients rotated to their left. This design was intentionally adopted in order not to compromise the quality of either the hemodynamic or echocardiographic measurements. Minor differences in hemodynamics or Doppler signal velocities may have been present between the supine and rotated positions. However, because control and nitroglycerin measurements were compared in the same postures, this aspect of the study design is unlikely to have altered the conclusions of the study.

Third, left atrial pressure was not directly measured, but was represented by pulmonary capillary wedge pressure, because transseptal puncture to obtain direct measurements of left atrial pressure was felt to be ethically unjustified. It is likely that directly measured crossover pressures would have yielded better correlations with the Doppler measurements.

Fourth, we assumed that the orifice of the mitral anulus is circular (29). We also employed a constant mitral anulus diameter throughout diastole to avoid introducing random error arising from making multiple measurements of the anulus. Ormiston et al. (36) previously showed that the mitral anulus diameter in humans is not constant, but increases by approximately 15% from early to late diastole, and then decreases during atrial contraction. Despite the use of these assumptions, the results of this study and previous work from this and other laboratories (29,33) demonstrated a good correlation between filling volume measured in this way and stroke volume measured by thermodilution.

Fifth, the heart rate was not controlled, and increased by an average of 5 beats/min during nitroglycerin infusion. A change in heart rate of this magnitude is by itself very unlikely to have produced the changes in the Doppler measurements that were observed. In a recent preliminary report (37), an increase in heart rate from 60 to 70 beats/min by atrial pacing did not alter the peak velocity of the E wave and decreased the velocity-time integral of the E wave less than the change observed in the present study (-9 versus -16%).

Sixth, we did not specifically study the effects of preload reduction on left ventricular filling in normal unmedicated subjects, because of the difficulty in obtaining such subjects for invasive study in our laboratory. Most of the patients studied had coronary artery disease and were being treated with either beta-adrenergic or calcium channel blockers. Also, there was considerable variation in their ages, a factor recognized to influence the pattern of ventricular filling (7,38). Because all patients were used as their own controls, the conclusions of this study should not be affected by these considerations. However, although qualitative similarities are expected, care must be taken when extrapolating these conclusions to patient groups other than the one studied.

Clinical implications. Doppler echocardiography can now provide noninvasive, beat to beat measurements of the instantaneous velocity of blood flow across the mitral valve in humans and is being used increasingly for this purpose. These measurements can be made with relative ease, without requiring irradiation or producing hemodynamic effects. This technique therefore offers an excellent opportunity for the study of left ventricular filling in health and disease and should help the development of a clearer understanding of the relation between the pattern of left ventricular filling and left ventricular diastolic properties. The results of this study demonstrate that the pattern of left ventricular diastolic filling in humans, as measured by the Doppler mitral flow velocity profile, is significantly altered by a reduction in preload, in a manner that mimics the abnormalities associated with impaired diastolic function. Left ventricular filling pressure must therefore be taken into account when interpreting Doppler-derived indexes of left ventricular diastolic function.

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